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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,852	11/04/2003	Susumu Hirose	244855US0	5771

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
09/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/699,852	HIROSE ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 4 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 04/11/08 has been acknowledged and fully considered.

Claims 1-6 are pending and are examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action

The applicant has amended the claims 1 and 2 to recite "intact cell" (instead of living cell) to overcome rejections under 35 USC 112(1). However the recent claim amendment (intact cell) renders the instant claim rejected over the prior art of record as stated below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsumoto et al (Abstract IP-0545, 5th Annual Meeting of the Molecular Biology Society of Japan", Edition and Publication, November 25th 2002, page 513, *Ref. of record on PTO-1449*).

Invention is drawn to a method for detecting negatively supercoiled DNA in an intact cell using a biotinylated psoralen probe. Matsumoto et al teaches visualization of DNA supercoiling and transcription in situ. The cited art teaches the bonding of psoralen to polytene chromosomal DNA in Drosophila salivary glands. The cited art teaches the biotinylated psoralen mediated cross-linking of DNA followed by the detection of the

cross-linking sites under an optical microscope using fluorescence-labeled avidin probes. The cited art further teaches that the cross-link formation occurs at high frequency in regions with low DNA density on a polytene chromosome. Frequency of cross-linking attributed to psoralen was lowered when transcription was inhibited by α-amanitin. Reduction in frequency of cross-linking was also observed when DNA was irradiated with X- rays to thereby introduce nicks therein and relax supercoils. The cited art concluded that the cross-link formation is considered to serve as an index of accumulation of negative supercoils in DNA strands. Thus given the broadest reasonable interpretation, the cited art clearly anticipates the invention as claimed.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Saffrin et al (US 4,868,311, 1989, *Ref. of record*).

Invention is drawn to a method for detecting negatively supercoiled DNA in an intact cell using a biotinylated psoralen probe. Saffrin et al teaches biotinlayted-psoralen (BPsor) which cross-links to DNA in the presence of UV rays (col. 9, lines 45-55). The cited art further teaches that BPsor binds covalently to DNA in a near UV photoreaction, resulting in interstrand crosslinks, and like other biotinylated molecules it binds to avidin, even after it has been incorporated into DNA. The cited art further teaches that the biotinylation does not interfere with its biological activity in lymphocytes. The cited art further teaches that the delivery of BPsor to cells as an avidin-BPsor conjugate (col. 5 lines 12-34; col.12 lines 24-68). The cited art teaches a lymphocyte proliferation assay, wherein the BPsor, was added to cells to a final concentration of 1 to 1000 ng/ml. After 20 minutes for drug uptake, 200 microliters of the cell suspension was added to wells in microtiter plates (Col.10, lines 21-54, col.12 table-1). The cited art further teaches that the BPsor binds covalently to DNA in a near UV photoreaction, resulting in interstrand crosslinks, and like other biotinylated molecules it binds to avidin, even after it has been incorporated into DNA. The biotinylation does not interfere with its biological activity in lymphocytes; treatment with BPsor at 10 ng/ml plus near UV light inhibits PHA stimulation (Col. 12, lines 24-34). The cited art further teaches that the inclusion of a

biotin group in psoralen enables the detection of psoralen derivatives with the exquisite sensitivity characteristic of the avidin-biotin interaction. Avidin-biotin systems have been developed with fluorescent, heavy metal, radioactive, immunological, and enzymatic labels. These labels allow measurement in a variety of systems, such as ELISA, filter hybridization, and microscopy of cells and tissue slices of isolated cellular components. The cited art clearly teaches the detection of localization of BPsor within cells by microscopy, using fluorescent or enzymatic labels (col.12, lines 35-49). Thus given the broadest reasonable interpretation, the cited art clearly anticipates the invention as claimed.

Claim Rejections - 35 USC § 103

Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsumoto et al (Abstract IP-0545, 5th Annual Meeting of the Molecular Biology Society of Japan", Edition and Publication, November 25th 2002, page 513, *Ref. of record on PTO-1449*) as applied to claims 1-3 above, and further in view of Chevalier et al (J Histochem. Cytochem. 45(4):481-91, 1997, *Ref. of record*).

The teaching of Matsumoto et al (2002) has been described above. Even though the Matsumoto et al teaches the visualization of DNA supercoiling and transcription in situ using biotinylated psoralen, the cited art does not teach the use of cell membrane permeation promoting agents.

Chevalier et al provides a review for in situ hybridization (ISH) techniques using biotinylated probes. The cited art further teaches that biotin, a small vitamin molecule (M_r 244), binds with high affinity to avidin, a protein largely distributed in egg whites (M_r 70,000), which can be conjugated to different markers such as fluorescent dyes, peroxidase, ferritin, and colloidal gold (page 482, col.1 para.3). The cited are further teaches permeabilization of cells or tissue section using permeation-promoting agent (page 484, col.1 para.2; page 488, col.1 para. 4). The cited art further teaches the detection of tissue or cells containing DNA of interest using biotinylated probes (see Fig. 4-6).

Thus it would have been obvious to one ordinary skilled in the art at the time the instant invention was made to modify the invention of Matsumoto et al by incorporating the cell membrane permeation promoting agents in view of Chevalier et al. One would have been motivated to do so to improve the intracellular delivery of the biotinylated psoralen in a specimen of interest (fixed). One would have a reasonable expectation of success, since the use of biotin-avidin system in conjunction with cell membrane permeation promoting agents for intra cellular detection of target moieties has been routine in the art at time the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saffrin et al (US 4,868,311, 1989, *Ref. of record*) as applied to claims 1-3 above, and further in view of Chevalier et al (J Histochem. Cytochem. 45(4):481-91, 1997, *Ref. of record*).

The teaching of Saffrin et al (1989) has been described above. Even though the Saffrin et al teaches the visualization of DNA supercoiling and transcription in situ using biotinylated psoralen, the cited art does not teach the use of cell membrane permeation promoting agents.

Chevalier et al provides a review for in situ hybridization (ISH) techniques using biotinylated probes. The cited art further teaches that biotin, a small vitamin molecule (M_r 244), binds with high affinity to avidin, a protein largely distributed in egg whites (M_r 70,000), which can be conjugated to different markers such as fluorescent dyes, peroxidase, ferritin, and colloidal gold (page 482, col.1 para.3). The cited are further teaches permeabilization of cells or tissue section using permeation-promoting agent (page 484, col.1 para.2; page 488, col.1 para. 4). The cited art further teaches the detection of tissue or cells containing DNA of interest using biotinylated probes (see Fig. 4-6).

Thus it would have been obvious to one ordinary skilled in the art at the time the instant invention was made to modify the invention of Saffrin et al by incorporating the

cell membrane permeation promoting agents in view of Chevalier et al. One would have been motivated to do so to improve the intracellular delivery of the biotinylated psoralen in a specimen of interest (fixed). One would have a reasonable expectation of success, since the use of biotin-avidin system in conjunction with cell membrane permeation promoting agents for intra cellular detection of target moieties has been routine in the art at time the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sumesh Kaushal
Primary Examiner
Art Unit 1633

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